Challenges in the use of preventive cardiovascular medications in Indonesia and the Netherlands

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ADDENDUM

SUMMARY
NEDERLANDSE SAMENVATTING
ACKNOWLEDGMENT
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SUMMARY

Cardiovascular disease (CVD) is a leading cause of morbidity and mortality worldwide. More than 75% of CVD-related deaths, mainly due to coronary heart disease (CHD) and stroke, take place in the low and middle-income countries (LMICs), including Indonesia. While CVD is no longer the main cause of hospitalizations or death in the Netherlands, one of the high-income countries (HICs), it is still the primary cause of death in Indonesia. To reduce the burden of CVD, the World Health Organization (WHO) and international cardiovascular (CV)-related organizations issue clinical guidelines that recommend, amongst other measures, the use of preventive CV medications based on an individual CV risk assessment. There are several classes of preventive CV medications recommended with evidence of effectiveness in CVD prevention and control. These medications are antithrombotic agents (aspirin, $P_{12}Y_{12}$ inhibitors, anticoagulants), antihypertensive agents (e.g., beta blockers, angiotensin-converting enzyme inhibitors [ACEIs], angiotensin receptor blockers [ARBs]) and lipid lower agents, e.g., statins. To optimize the use of these preventive medications in populations at risk remains a challenge. These challenges are different in Indonesia as an LMIC and the Netherlands as an HIC. Studies on the effectiveness of these medications in an Indonesian population at risk of CVD are very limited. It has been reported that CVD-related guidelines and CV risk stratification are underutilized. Within the new National Health Insurance System (NHIS, namely *Jaminan Kesehatan Nasional-Kartu Indonesia Sehat* [JKN-KIS]) in Indonesia, the primary healthcare sector plays an important role to influence the use of preventive CV medications. Meanwhile, systematic and programmatic CVD prevention in the Netherlands has already been introduced since 2005. The role of the Dutch primary healthcare sector and health insurance companies in CVD prevention is prominent. The clinical guidelines to manage multi CV risk factors have already been developed since the mid-2000s. The differences in the stage in CVD prevention between both countries may result in distinct challenges related to the use of preventive CV medications in Indonesia and the Netherlands. This thesis aims to identify current challenges in the use of guideline-recommended CV preventive medications in Indonesia and the Netherlands. CHD is the type of CVD that we focus on. The thesis is divided into two parts: **Part 1** (**Chapter 2-5**) investigates the long-term CVD burden in Asians and the challenges in using preventive CV medications in Indonesia, and **Part 2** (**Chapter 6 and 7**) studies the challenges in using specific preventive CV medications in the Netherlands.

In **Chapter 2**, a systematic review and meta-analysis was conducted to estimate the long-term (> 10 year) risk of CVD and its risk factors in Asian populations. Most studies identified were from the East-Asian region, none was from Indonesia. The long-term risk of fatal CVD in the Asian populations was 6.35% during a 20.00 years of mean follow-up. The long-term risk of fatal stroke was higher than of fatal CHD. Different risk factors between CHD and stroke were identified. Men, older age and current smokers were risk factors for fatal CVD identied from the meta-analysis. In contrast to previous studies in Western populations, we concluded that different approaches might be necessary for CVD prevention and control in Asians due to the different burden and risk factors compared to Westerners.

In **Chapter 3**, a cohort study aimed to estimate the effectiveness of guideline-recommended preventive CV medications on in-hospital mortality in patients with ST-elevation myocardial infarction (STEMI), an acute manifestation of CHD, was conducted using the Jakarta Acute Coronary Syndrome (JAC) Registry. We observed the use of preventive medications in 42% patients with STEMI not treated with acute primary percutaneous coronary intervention (pPCI) therapy, the majority of whom were late presenters at the hospital. A third of these patients did not receive guideline-recommended preventive medications at hospital admission. After potential confounders were taken into account in the statistical analysis, it was estimated that the use of preventive CV medications in this population reduced the odds of in-hospital death by more than 50%.

In **Chapter 4**, using a cohort study from the same registry, we assessed predictors for suboptimal use of guideline-recommended preventive CV medications in patients with STEMI. We found the predictors were the presence of non-anterior MI; age > 65 years; not being treated with acute reperfusion therapy; having a family history of CAD; and having a thrombolysis in myocardial infarction (TIMI) score ≥ 4. Not being treated with reperfusion was identified as the common predictor for not receiving most drug classes separately.

From both **Chapter 4** and **5**, it seemed there was a presence of treament-risk paradox, a situation where patients with higher risk tended to receive less medications compared to patients with low risk. Since there is no specific risk stratification for patients with STEMI, we suggested physicians might have different perceptions on the

benefit-risk of using guideline-recommended medications for different patient groups, hence a more personalized approach is required.

In **Chapter 5**, a qualitative study was conducted to elicit physician's perspective on factors influencing the decision to prescribe statins as part of CVD prevention and control. These factors were mapped into a research-based framework analysing the use of statins by general practitioners in England. We found factors operating at microlevel (patient' characteristics, physician' professional experience) and macrolevel (NHIS, international references) contributed to physicians' decision making to prescribe statins. We could not identify any factors from mesolevel as observed in England. It was concluded that the role of primary healthcare in CVD prevention was still limited, because of the relatively recent introduction of the NHIS in Indonesia.

In **Chapter 6**, disparities in the effects of statins on lipid parameters between Dutch men and women were investigated in an inception cohort study using the PharmLines Initiative database. Limited by the small sample size, we found that regardless of the presence of previous CVD, statin therapy increased the level of high-density lipoprotein cholesterol (HDL-c) from baseline more significantly in women than in men. However, the proportion of both men and women who achieved the guideline-recommended low-density lipoprotein cholesterol (LDL-c) target was less than 40% suggesting more investigation on the interplay between statin dose and the level of adherence in statin users that might influence the achievement of this target.

In **Chapter 7**, an inception cohort study using the same database, the association between adherence to statin therapy and lipid parameter response was estimated in first-time statin users on standard dose and low dose. We found the level of adherence to statin therapy was similarly associated with the LDL-c response between standard- and low-dose users. However, with regards to sex, the same level of adherence was associated with a significantly faster rate of reduction of LDL-c in women than in men. This disparity between sexes was also observed in the subgroup of statin standard-dose, but not in the subgroup of low-dose.

In **Chapter 8**, we described how our findings may influence clinical practice and future research. It is apparent that more investigations in the form of longitudinal and quantitaive studies are needed to estimate the burden of CVD and the use of

preventive medications in Indonesia. The local clinical guideline needs to be more promoted and its implementation needs to be optimized by addresing factors hindering the use of guideline-based preventive CV medications, including the needs of risk stratification to guide the treatment. Opportunities to enhance the role of primary healthcare in CVD prevention and control in Indonesia within the new NHIS scheme needs to be discussed and established. In the Dutch setting, there is a need for a slight improvement on the achievement of the target using statins in order to optimize CVD prevention. A database linkage between population-based and dispensing database provides an oportunity to investigate more important variables (e.g. patients' adherence, dose of medications) influencing the optimal use of CV preventive medications such as statins in the Netherlands. The possibility of sex disparities in the effect of statins on lipid parameters needs further study with a larger sample size including patients' level of adherence and the fluctuation of statin dose over the period of follow-up.

Samenvatting

Hart- en vaatziekten (Engels: CardioVascular Diseases (CVD)) behoren tot de hoofdoorzaak van ziekte en sterfte wereldwijd. Meer dan 75% van CVD-gerelateerde sterfgevallen, met name door coronaire hartziektes (CHD) en beroertes, vinden plaats in lage- en middeninkomenslanden (LMICs), waaronder Indonesië. Hoewel CVD niet langer de hoofdoorzaak is van ziekenhuisopnames en sterfgevallen in Nederland, een van de hoge-inkomenslanden (HILs), is het nog steeds een hoofdoorzaak van sterfgevallen in Indonesië. Om de druk van CVD te verlichten, hebben de World Health Organization (WHO) en internationale cardiovasculaire (CV-)gerelateerde organisaties klinische richtlijnen opgesteld die onder andere aanraden om preventieve CV-medicijnen te gebruiken gebaseerd op een individuele CV risicobeoordeling. Er zijn verschillende klassen van preventieve CV-medicijnen die aanbevolen worden met bewezen effectiviteit in het voorkomen van CVD. Deze medicijnen zijn antitrombose-middelen (aspirine, $P_{I2}Y_{I2}$ inhibitors, antistollingsmiddelen), antihypertensie-middelen (bijv., bètablokkers, remmers van angiotensineconverterend enzym [ACE-remmers], angiotensine receptor blokkers [ARBs]) en cholesterolverlagende medicamenten, zoals statines. Het blijft een uitdaging om het gebruik van deze preventieve medicijnen te optimaliseren in een risicopopulatie. Deze uitdagingen zijn anders in Indonesië als LMIC dan in Nederland als HIL. Onderzoek naar de effectiviteit van deze medicijnen in de CVD-risicopopulatie van Indonesië is erg beperkt. De primaire gezondheidszorgsector in de nieuwe National Health Insurance System (NHIS, namelijk de *Jaminan Kesehatan Nasional-Kartu Indonesia Sehat* [JKN-KIS]) in Indonesië, speelt een belangrijke, invloedrijke rol in het gebruik van preventieve CV-medicijnen. In Nederland is systematische en programmatische CVD-preventie echter al in 2005 geïntroduceerd. De Nederlandse primaire gezondheidszorgsector en zorgverzekeringsmaatschappijen spelen een belangrijke rol bij CVD-preventie. De klinische richtlijnen die risicofactoren voor CV toeppassen, zijn al in ontwikkeling sinds mid-2000. Het verschil tussen de stadia van CVD-preventie in beide landen kan resulteren in specifieke uitdagingen qua gebruik van preventieve CV medicijnen in Indonesië en Nederland. Deze dissertatie beoogt de huidige uitdagingen in het gebruik van preventieve CV-medicijnen op basis van aanbevolen richtlijnen in Indonesië en Nederland te identificeren. CHD is het hoofdtype CVD waar we in ons onderzoek op focussen. Deze dissertatie is opgedeeld in twee gedeeltes: **Deel 1 (Hoofdstuk 2-5)** onderzoekt de langdurige CVD druk bij Aziaten en de uitdagingen bij het gebruik van preventieve CV-medicijnen in Indonesië, en **Deel 2 (Hoofdstuk 6**

en 7) onderzoekt de uitdagingen bij het gebruik van preventieve CV-medicijnen in Nederland.

In **Hoofdstuk 2** is een systematische evaluatie en meta-analyse beschreven om vast te stellen wat het lange-termijnrisico (> 10 jaar) is van CVD en de risicofactoren in Aziatische bevolkingsgroepen. De meeste onderzoeken die hier omschreven worden, zijn toegespitst op de Oost-Aziatische regio, geen enkele kwam uit Indonesië. Het lange-termijnrisico van fatale CVD in de Aziatische bevolkingsgroep is 6.35% tijdens een gemiddelde duur van 20 jaar. Het lange-termijnrisico van een fatale beroerte is hoger dan dat van fatale CHD. Verschillende risicofactoren tussen CHD en beroertes worden omschreven. Risicofactoren voor fatale CVD die geïdentificeerd zijn met behulp van de meta-analyse zijn: het mannelijk geslacht, hogere leeftijd, roken. In tegenstelling tot voorgaande onderzoeken onder de Westerse bevolking, kwamen wij tot de conclusie dat andere methodes misschien nodig zijn voor CVD-preventie en controle in Aziaten vanwege de verschillende uitkomsten en risicofactoren in vergelijking met Westerlingen.

Hoofdstuk 3 beschrijft een cohortonderzoek met als doel de effectiviteit vast te stellen van preventieve CV-medicijnen op basis van aanbevolen richtlijnen ten aanzien van ziekenhuissterfte bij patiënten met hartinfarct met ST-elevatie (STEMI), een acute manifestatie van CHD. Deze studie is uitgevoerd met behulp van het Jakarta Acute Coronary Syndrome (JAC) Register. We zien het gebruik van preventieve medicijnen bij 42% van de patiënten met STEMI die niet behandeld werden met 'acute primaire percutane coronaire interventie (pPCI)' therapie, van wie het merendeel laat in het ziekenhuis arriveerde. Eenderde van deze patiënten kregen geen preventieve medicijnen op basis van aanbevolen richtlijnen bij opname in het ziekenhuis. Nadat er rekening is gehouden met mogelijke verstorende factoren in de statistische analyse, werd geschat dat het gebruik van preventieve CV-medicijnen in deze bevolkingsgroep het overlijdensrisico in het ziekenhuis kan verlagen met meer dan 50%.

In **Hoofdstuk 4**, met het gebruik van een cohortonderzoek uit hetzelfde register, evalueren we de predictoren voor suboptimaal gebruik van preventieve CV-medicijnen op basis van aanbevolen richtlijnen bij patiënten met STEMI. We ontdekten de volgende predictoren: de aanwezigheid van non-anterior MI; leeftijd > 65 jaar; geen behandeling met acute reperfusietherapie; een familiegeschiedenis met CAD;

een trombolyse in myocard infarct (TIMI) score ≥ 4. Het niet behandeld zijn met reperfusie was geïdentificeerd als de predictor voor alle geneesmiddelklassen.
In zowel **Hoofdstuk 4** als **5** leek een treatment-risk paradox te bestaan, dit is een situatie waarbij patiënten met een hoger risico minder medicatie krijgen in vergelijking met patiënten met een lager risico. Omdat er geen specifieke risicostratificatie voor patiënten met STEMI is, suggereren wij dat artsen mogelijk verschillende perspectieven hebben op het risico of profijt dat het gebruik van medicijnen op basis van richtlijnen met zich meebrengt voor verschillende patiëntengroepen. Hierdoor is een gepersonaliseerde aanpak nodig.

Het kwalitatief onderzoek in **Hoofdstuk 5** toont het perspectief van een arts op de factoren die van invloed zijn op de beslissing om statines voor te schrijven bij CVD-preventie en controle. Deze factoren zijn gebaseerd op een research-based raamwerk dat het gebruik van statines bij huisartsen in Engeland analyseert. We ontdekten factoren die op microlevel opereren (eigenschappen van patiënten, professionele ervaring van de behandelend arts) en op macrolevel (NHIS, internationale richtlijnen) welke allemaal bijdroegen aan de beslissing van de arts om statines voor te schrijven. We hebben geen factoren kunnen identificeren op mesolevel zoals in Engeland. Er werd geconcludeerd dat de rol van de primaire gezondheidszorg in CVD-preventie nog steeds gelimiteerd is, vanwege de relatief recente invoering van de NHIS in Indonesië.

In **Hoofdstuk 6** worden de verschillende effecten van statines op lipide-parameters tussen Nederlandse mannen en vrouwen onderzocht in een inceptie-cohort studie met gebruik van de PharmLines Initiative database. Ondanks de gelimiteerde grootte van onze testgroep, hebben we toch aan kunnen tonen dat ongeacht de aanwezigheid van eerdere CVD, statine therapie de concentratie van high-density lipoproteine cholesterol (HDL-c) sinds start van medicatie significanter verhoogde in vrouwen dan in mannen. Echter, het aantal mannen en vrouwen dat de aanbevolen low-density lipoproteine cholesterol (LDL-c) doel behaalde was voor beide geslachten lager dan 40%. Dit suggereert dat meer onderzoek naar de interactie tussen statine dosering en mate van adherence in statinegebruikers nodig is in het behalen van de doelstelling. Een inceptie-cohortonderzoek met dezelfde PharmLines database is gebruikt in **Hoofdstuk 7** om het verband tussen adherentie aan statinetherapie en lipide parameter response te berekenen bij nieuwe gebruikers voor een standaard dosering

en lage dosering. We ontdekten dat het adherentie niveau voor statine therapie evenwijdig gerelateerd was aan de LDL-c response tussen de standaard- en lage-dosering-gebruikers. Maar als we naar geslacht kijken, zagen we hetzelfde adherentie niveau geassocieerd met een significant snellere reductie van LDL-c bij vrouwen dan bij mannen. Deze ongelijkheid tussen de geslachten werd ook geobserveerd in de subgroep van standaard statine dosering, maar niet in de subgroep van de lage dosering.

In **Hoofdstuk 8** beschrijven we hoe onze bevindingen mogelijk van invloed kunnen zijn op de klinische praktijk en toekomstig onderzoek. Het is duidelijk dat er meer onderzoek moet worden gedaan in de vorm van longitudinaal en kwantitatief onderzoek om de ziekte en sterftelast van CVD en het gebruik en effecten van preventieve medicijnen in Indonesië goed in te kunnen schatten. De lokale, klinische richtlijnen moeten gepromoot worden en de implementatie hiervan moet geoptimaliseerd worden door factoren aan te pakken die het gebruik van preventieve CV-medicijnen op basis van richtlijnen hinderen, waaronder de wens om risicostratificatie te gebruiken bij een behandeling. Mogelijkheden om de rol van de primaire gezondheidszorg te vergroten bij CVD -preventie en bestrijding in Indonesië binnen het nieuwe NHIS systeem, moeten worden besproken en vastgelegd. In Nederland is er behoefte aan verbetering van het halen van de doelstellingen ten aanzien van cholesterol verlaging met statine om CVD-preventie te optimaliseren. De huidige database link tussen Lifelines en de geneesmiddeldatabase van de Universiteit Groningen biedt een mogelijkheid om de belangrijkste variabelen te onderzoeken (bijvoorbeeld adherentie van patiënten, dosering van medicatie) die het optimale gebruik van CV preventie medicijnen beïnvloeden in Nederland. Mogelijke verschillen door geslacht bij het effect van statines op lipide parameters verdient verder onderzoek met een grotere testgroep waarbij ook het adherentie-niveau van patiënten en de fluctuatie van statine dosering tijdens de follow up worden betrokken.

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ABOUT THE AUTHOR

Sylvi Irawati was born in Malang, East Java, Indonesia. She obtained her bachelor's degree in Pharmacy at the Faculty of Pharmacy, Universitas Surabaya, Surabaya, Indonesia in 2003. She finished her professional degree in Pharmacy, major in Clinical Pharmacy, in 2004 at the same university. She worked as a researcher at the Department of Research & Development in a local pharmaceutical industry in Surabaya, formulating liguid vitamins and injections, from 2004 to 2006. She, then, pursued her master's degree in Clinical Pharmacy at the same university from 2006 to 2008. She graduated with *cum-laude* from all her educations. She has been working as a drug information pharmacist and researcher at the Centre for Medicines Information & Pharmaceutical Care (CMIPC/Pusat Informasi Obat dan Layanan Kefarmasian, PIOLK), Universitas Surabaya, since 2007 and as a lecturer at the Department of Clinical & Community Pharmacy, Faculty of Pharmacy of the university since 2011. She is a member of the Commitee of Pharmacy and Therapeutic and a visiting clinical pharmacist at the St. Vincentius a Paulo Hospital, Surabaya, since 2009, through a collaboration between CMIPC and the hospital. Her interest in research and lecture is mainly in the use of cardiovascular medications in the hospital and community. She started her PhD track under the supervision of Prof. Eelko Hak and Prof. Katja Taxis in March 2016 at the Department of of Pharmaco-Therapy, -Epidemiology & -Economics (PTE2), University of Groningen, the Netherlands. Her PhD project was funded by the Indonesia Endowment Fund for Education (Lembaga Pengelola Dana Pendidikan, LPDP) and focused on the challenge in the use of cardiovascular medications in Indonesia and the Netherlands. After completing her PhD, she will continue her work at Universitas Surabaya.

PhD PORTFOLIO

Name	:	Sylvi Irawati
Unit of PhD	:	Department of Pharmaco-Therapy, -Epidemiology & –Economics, Groningen Research Institute of Pharmacy (GRIP), University of Groningen, the Netherlands.
PhD period	:	2016-2020
Promotors	:	Prof. Eelko Hak
		Prof. Katja Taxis

Courses/ Workshops	**Year**	**Workload (hours/ ECTS)**
Internal		
Data handling and pharmacoepidemiology in practice	2016	5
Pharmacoeconomics	2016	5
Presentation skills	2016	0.5
Systematic review and meta-analysis	2016	1
Scientific integrity	2016	2.5
Pharmacoepidemiology UK	2016	5
Managing your PhD	2016	2
Basic Medical statistics	2017	3
Study design in clinical epidemiology	2017	4
Science writing	2017	2
Publishing in English	2017	3
Advance topics in pharmacoepidemiology	2017	5
Epidemiology and applied statistics	2018	3
Quality-of-Life and Patient-Reported Outcome Measures (QoL & PROMs)	2019	2.5

External		
Medical Sciences Summer School, University Medical Center Groningen, Groningen, the Netherlands: fundamentals of biobanking and cohort research.	2017	Not available
Pre-conference courses of the 34th International Conference on Pharmacoepidemiology & Therapeutic Risk Management (ICPE), Praque, Czech Republic: Advanced drug utilization research Using field studies to value-add in pharmacoepidemiology Best practices for designing, implementing and evaluating risk minimization programs	2018	Not available
European Consortium for Political Research (ECPR), Budapest, Hungary: survey and questionnaire design.	2019	4

Published and submitted article in scientific journals

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